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APPLICATION NUMBER: *60/508,830*
FILING DATE: *October 03, 2003*
RELATED PCT APPLICATION NUMBER: *PCT/US04/32008*

Certified by

Jon W Dudas

Acting Under Secretary of Commerce
for Intellectual Property
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PTO/SB/16 (05-03)
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. EE733673865US

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Chris T.	Zimmerle	Goshen, IN

Additional inventors are being named on the _____ *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

Method for Increasing Precision of Reflectance Measurements

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☑ Customer Number: 37486

OR

☑ Firm or Individual Name	Elizabeth A. Levy				
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ENCLOSED APPLICATION PARTS ***(check all that apply)***

☑ Specification *Number of Pages* 8 ☐ CD(s), Number _____

☐ Drawing(s) *Number of Sheets* _____ ☐ Other (specify) _____

☐ Application Date Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check or money order is enclosed to cover the filing fees.

☑ The Director is herby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 50-0781

☐ Payment by credit card. Form PTO-2038 is attached.

FILING FEE Amount ($): 160.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☑ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE _____

TYPED or PRINTED NAME Elizabeth A. Levy

TELEPHONE 508-359-3876

Date Oct 3, 2003

REGISTRATION NO. 34,375 *(if appropriate)*

Docket Number: MSA-3462

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Attorney Docket No.: MSA-3462

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PROVISIONAL APPLICATION FOR PATENT

TITLE: METHOD FOR INCREASING PRECISION OF REFLECTANCE MEASUREMENTS

INVENTOR: Chris T. Zimmerle

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that, on the date shown below, this correspondence, and any attachments referred to herein, are being deposited with the United States Postal Service in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 under 37 CFR 1.10 as "Express Mail Post Office to Addressee" Mailing Label No.: EE733673865US.

Gayle Gestick

10/3/03
Date

1540X

MEMO OF INVENTION

(Transmit in Quadruplicate to Legal Department)

A. Brief descriptive title.

A Method for increasing the precision of reflectance measurements

B. Project No. Project Name:

C. This invention relates to: (Circle as many as seem applicable.)

(2) a process (production, fabrication, use, treatment, etc.),

D. State the anticipated commercial application of the invention.

The detection and measurement of analyte(s) by reflectance measurements.

E. State precisely what your invention is. Indicate what problem was solved and how you solved it. (Attach relevant technical publications discussing the problem).

Improved intra-assay precision results from correcting reflectance readings of a colored particle or substance by using a ratio of a known reflectance constant to the actual measured value at a wavelength removed from the colored particle and substance and unaltered by changes in concentration of that particle or substance..

There are numerous rapid test assays in the market utilizing immunochromatography devices. Most are limited to YES / NO answers because of their poor quantitation. To achieve a higher level of quantitation, reflectance meters can be used to subjectively examine the colored bands formed. Reflectance measurements are prone to many sources of error because the strip positioning and height can greatly alter the amount of photons reaching the detector. For instance, slight differences in height will alter the reflectance value obtained, thus adding a source of error when measuring analyte concentration by reflectance measurements. By choosing a wavelength which does not undergo any change in signal with increasing analyte concentration it is possible to ratio the wavelengths and remove this error. This has been commonly done in many of the present MULTISTIX test. The problem with just ratioing the wavelengths is that numbers are obtained which have great difficulty in associating meaning to and impossible to transform to K/S, a common algorithm used to linearize reflectance measurements. This method allows the benefit of wavelength ratioing AND ability to subsequent transformations.

F. How have others tried to solve this problem in the past and why were the prior attempts unsuccessful?

Wavelength ratioing has been used but gives values which are no longer reflectance measurements and difficult to interpret. These values are also not

possible to transform to K/S, a common function for relating reflectance values to analyte concentration.

G. Indicate whether a literature and/or patent search has been performed, and if so, the nature and extent of such search.

No patent search was performed.

Whether or not a search has been performed, list the references, patents, existing products, etc. which you believe to be most relevant to the invention.

MOI 15362 - Use of a calibration line with known reflectance properties to correct for errors.
MOI 15439 - Device & method to obtain clinically significant analyte ratios.
MOI: Methods for Reduction of between instrument variation recently submitted by

H. State how your invention differs (functionally and/or structurally) from the items listed in G. List the advantages which your invention has over same.

MOI 15362.
A method using a calibrated color stripe of known reflectance value to correct out for instrument to instrument differences. A separate colored stripe was used as a reference band to correct errors in reflectance readings. Compared to this MOI, wavelengths are not ratioed and a separate calibration stripe is not used. It is the author's belief that both methods are important to allow the highest accuracy in reflectance readings; one method reduces instrument to instrument error while the other method reduces intra-instrument error.

MOI 15439:

The aspect of reducing reflectance measurement error as given in this MOI is referenced in MOI 15439.

MOI: Methods for Reduction of between Instrument Variation:

This MOI corrects out instrument to instrument differences using an empirically-derived factor, I, and was shown for those examples to be superior to the method here. The equation given in that MOI

$$[Rn] = [\%R] * I$$

where:

Rn is the corrected % reflectance
I is the factor derived to give the minimum bias between instruments
R is the reflectance

can be contrasted with the equation given in this MOI. Two wavelengths are required for this MOI, one of the wavelengths having no signal related to increasing analyte concentration. The wavelength constant used in this MOI is derived from experimentally determining the average or known reflectance. Instrument to instrument error will not be reduced by using the method shown here unless there is correlation between filter variations of the instruments.

I. Briefly describe how your machine operates, your process is carried out or your product is made and used. If possible, attach a drawing and refer to the drawing to describe how your invention works.

The IR correction constant is used on the CT50 to reduce between strip error. The strip background in the IR region (around 900 nm) has no reflectance due to the binding chemistry, thus changes in the reflectance are assumed to be due to variations in the membrane, instrument, or strip orientation (height). Variations in reflectance caused by these variations often are observed at all wavelengths thus altering the reflectance of the band peaks. By using a known value for the IR (usually around 75% for a wet nitrocellulose membrane affixed to MULTISTIX polystyrene), variations in all the wavelengths can be corrected by using the ratio as already described in the MOI. Raw reflectance values used in any algorithm are adjusted in this manner before incorporating into any specific algorithm. The wavelength used for the corrections does not necessarily have to be the IR, only a wavelength which demonstrates no reflectance changes at the band peak locations. To illustrate an example, a 7 sample 3 replicate run of PSA gave the following reflectance's before and after IR correction.

	Raw %R SD (pooled from all levels)	**Corrected %R SD (pooled from all levels)**	**Fold reduction in %R SD**
Capture Band	2.0	1.14	1.75
Collection Band	1.85	0.67	2.76

Reflectance is corrected by using the following equation:

$$R_{\lambda c} = [\ R_{\lambda\text{-const}} * R_{\lambda}\ ] / R_{\lambda\text{-meas}}$$

where

- $R_{\lambda c}$ is the corrected reflectance value for a given wavelength or broad band filter, λ
- $R_{\lambda\text{-const}}$ is the corrected reflectance value constant for the wavelength unresponsive to analyte concentration. For wet nitrocellulose this has been assigned the value of 75%. This value is assigned by averaging numerous runs and obtaining the average reflectance for it. For gold sol labeled conjugate the IR wavelength is appropriate because little or no IR reflectance is associated with this label. The reference wavelength chosen can be a wavelength other than the IR, but it should not exhibit any signal changes associated with increasing analyte concentration.

- R_{λ} is the observed reflectance value measured using the wavelength with the highest signal to noise.
- $R_{\lambda\text{-meas}}$ is the observed reflectance value through the IR filter, the wavelength which demonstrates no signal changes due to increased analyte concentration.

We have determined that IR correction removes error between replicate readings and is important in increasing the signal to noise ratio. An example of this is shown in Table 2 below. In this example the error (given by the SD) was reduced nearly 75%.

Table 2. Example of using the IR-correction to increase the signal to noise ratio. N=12

	First Capture Zone				First Collection Zone			
[DPD]	Raw		IR cor		Raw		IR cor	
	%R	*SD*	*%R*	*SD*	*%R*	*SD*	*%R*	*SD*
0	63.1	1.1	62.6	0.5	76.9	2	73.7	0.5
10	62.5	1.5	63.6	0.3	75.2	2.3	73.7	0.7
25	67.2	2.3	66	0.5	70	2.5	67.5	0.5
75.	67.1	1.7	67.9	0.6	60.2	2.1	60.4	0.6
150	71.1	3.2	71.1	0.7	60	2.8	60.2	0.8
250	72.7	2.4	71.8	0.4	61.4	2.1	60.5	0.6
AVG		2.0		0.5		2.3		0.6

The corrected reflectance data can then be transformed to K/S through the following equation:

$$K/S(R_c) = (1-R_c)^2 / (2R_c)$$

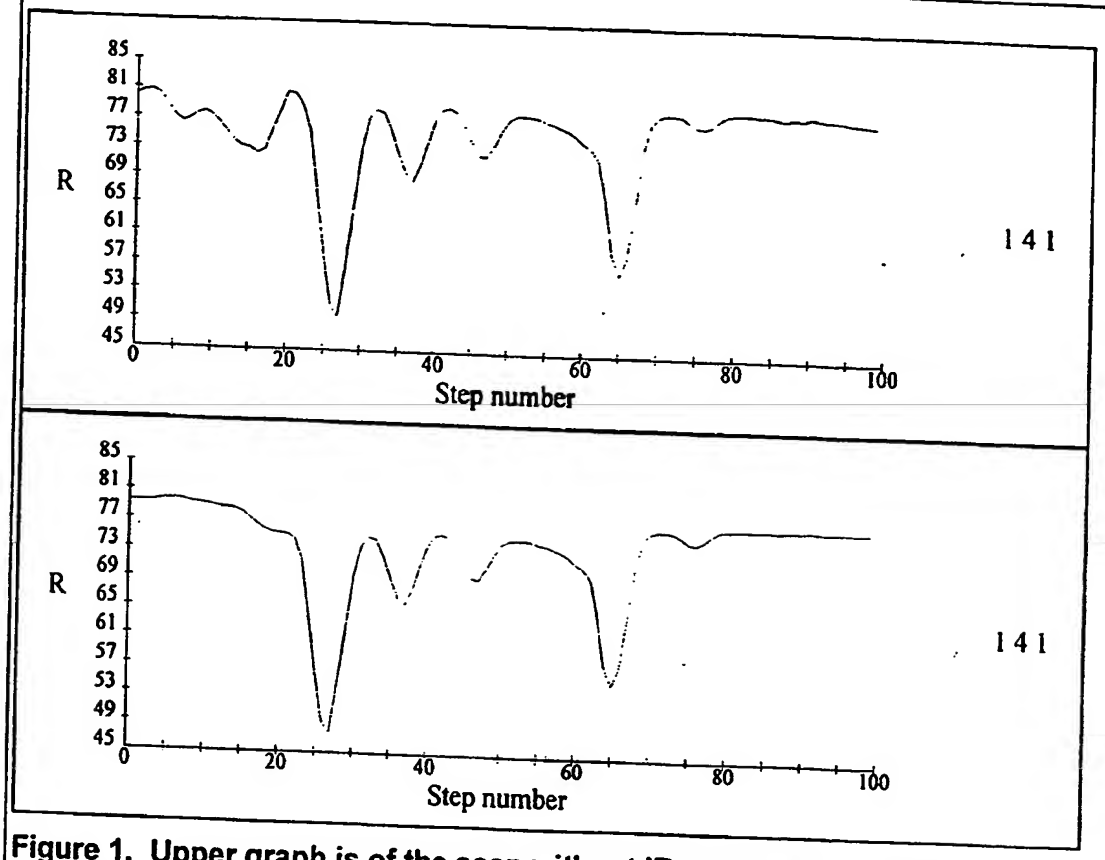

Figure 1. Upper graph is of the scan without IR correction, the lower scan is with IR correction.

K. When did you first think of the invention?

Identify the records you have to substantiate this date, including books, letters, notes, reports, etc.

For strip pads:
RB 20501-18

For Nitrocellulose-based iimunostrip readings:
RB25262-01
Group Update

L. To whom did you first disclose (orally or in writing) this invention?

On what date and where did you make such disclosure?

What written evidence do you have of making this disclosure to others?

M. When did you first do any actual experimental work toward carrying out the invention? (Identify laboratory notebooks by number and page.)

For MULTISTIX pads: *RB20501-18 to 29*
For Nitrocellulose immunostrips: *RB25262-01 to 07*

When did you first demonstrate the operation of the invention performing its intended function (i.e., a demonstration of utility or a demonstration of pharmacological activity)?

For MULTISTIX pads: *RB20501-18 to 29*
For Nitrocellulose : RB25262-01 to 07

N. Who has observed the progress of your experimental work?

O. Identify all individuals who worked on the invention and indicate the nature of each individual's contribution. (Include inventors listed in this MOI.)

Name	Contribution
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

P. Identify any Memo of Invention (MOI) or patent application related to this invention.

MOI . Methods for Reduction of Between Instrument Variation

Q. Has any commercial manufacture, use or product sale begun?

____ Yes _X_ No If Yes, provide details.
When is commercial manufacture, use or any offer for sale anticipated?

UNKNOWN

R. Has any information concerning this invention been disclosed outside Bayer? (Include oral discussions with third parties, publications, advertising, market research, test marketing, etc.)

NO

Is any such outside disclosure anticipated? Explain.

NO

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World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse